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Contemporary hormonal contraception and cervical cancer in women of reproductive age

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Abstract

To determine cervical cancer risk associated with contemporary hormonal contraceptives, we conducted a cohort study of women aged 15 to 49 living in Denmark from 1995 to 2014, using routinely collected information about redeemed prescriptions, incident cancer and potential confounders. Poisson regression calculated adjusted cervical cancer risks among different contraceptive user groups by duration of use, time since last use, hormonal content and cancer histology. During >20 million person-years, 3643 incident cervical cancers occurred. Ever users of any hormonal contraceptives compared to never users had a relative risk (RR) of 1.19 (95% confidence interval [CI] 1.10-1.29). Increased risks were seen in current or recent users of any hormonal: RR 1.30 (95% CI 1.20-1.42) and combined: RR 1.40 (95% CI 1.28-1.53), but not progestin-only contraception: RR 0.91 (95% CI 0.78-1.07). Current or recent users of any hormonal contraception had an increased risk of both adenocarcinoma (RR 1.29, 95% CI 1.05-1.60) and squamous cancer (RR 1.31, 95% CI 1.19-1.44). The risk pattern among any hormonal and combined contraceptive users generally increased with longer duration of use and declined after stopping, possibly taking longer to disappear among prolonged users. Combined products containing different progestins had similar risks. Approximately one extra cervical cancer occurred for every 14 700 women using combined contraceptives for 1 year. Most women in our study were not vaccinated against human papillomavirus (HPV) infections. Our findings reinforce the urgent need for global interventions such as systematic screening, treatment of cervical intraepithelial neoplasia and HPV vaccination programmes to prevent cervical cancer, especially among users of combined contraceptives.

KEYWORDS
cervical cancer, cohort study, combined contraceptives, hormonal contraception, progestin-only

1 | INTRODUCTION

In 2018, approximately 570 000 new cases of cervical cancer (6.6% of all new female cancers), and 311 365 related deaths occurred worldwide.[1] A necessary cause of cervical cancer is human papillomavirus

Abbreviations: BMI, body mass index; CI, confidence interval; HPV, human papillomavirus; ICD, International Classification of Diseases; ICD-O-3, International Classification of Diseases for Oncology 3rd edition; LNG-IUS, levonorgestrel-releasing intrauterine system; OR, odds ratio; RR, relative risk; SIR, standardised incidence ratio.

(HPV) infection with eight types of HPV found in 91% of cases of cervical cancer worldwide.[2] Currently available bivalent, quadrivalent and nonavalent HPV vaccines provide the opportunity to prevent a large proportion of cervical cancer cases. More than 80% of all cervical cancer cases occur in Africa, Asia, Latin America and the Caribbean. Most countries within these regions do not have an HPV immunisation programme.[3,4] Vaccine shortages are ongoing and predicted to last at least until 2025[5] resulting in a large number of women around the world remaining at risk of HPV infection and cervical cancer.

Risk factors for cervical cancer include aspects of sexual behaviour, cigarette smoking, immunodeficiency and oral contraception.[6] In 2019, an estimated 151 million women of reproductive age worldwide used oral contraceptives, of which roughly two-thirds lived outside Europe, North America, Australia and New Zealand.[7] Thus, most oral contraceptive users live in countries without comprehensive HPV vaccination or cervical screening programmes. Past evidence, summarised by the International Collaboration of Epidemiological Studies of Cervical Cancer using pooled individual data from 24 studies worldwide, found that current and recent use of combined oral contraceptives, and possibly 5 or more years of progestin-only injectables, was positively associated with cervical cancer.[8] The risk strengthened with duration of use and waned after stopping, reaching that of never users by about 10 years after cessation. Most of the evidence included in the analysis, however, examined cervical cancer risk among the first generation of combined oral contraceptive users exposed to preparations containing a high (50 μg or more) or medium (30-35 μg) dose of oestrogen combined with an older progestin. Furthermore, the duration of use was relatively short. A more recent systematic review and meta-analysis restricted to nine heterogeneous studies did not find an altered cervical cancer risk among ever users of oral contraceptives, odds ratio (OR): 1.21, 95% confidence interval (CI) 0.91-1.61.[9] This meta-analysis, however, did not examine current or recent, or former, use separately. Another limitation was the inclusion of only studies published between 2000 and 2012, in an attempt to assess the effects of oral contraceptives similar to those currently marketed, although several reports were of long-term follow-up of women using older products.[10,11] Presently, there is very limited direct evidence informing users and their providers about whether contemporary hormonal contraceptives alter cervical cancer risk. We evaluated the risk of cervical cancer among users of hormonal contraception in a large cohort study of virtually all women of reproductive age and living in Denmark; most of whom had not been vaccinated against HPV.

What's new?

Globally, millions of hormonal contraception users are unvaccinated against human papillomavirus (HPV) infections, which are known to cause cervical cancer. Little is known about contemporary hormonal contraceptives and cervical cancer risk. In this cohort of mostly unvaccinated women, current or recent use of any hormonal and combined but not progestin-only contraceptives increased cervical cancer risk. The effect strengthened with increasing duration and took longer to decline with prolonged use. The results reinforce the urgency for global interventions to prevent cervical cancer including HPV vaccination programmes, systematic cervical screening and treatment of cervical intraepithelial neoplasia, especially among users of combined contraceptives.

2 | MATERIALS AND METHODS

The previously described Danish Sex Hormone Register Study[12,13] includes all women aged 15 to 79 years resident in Denmark and aims to investigate hormone use and cancer, cardiovascular and psychiatric diseases. For this analysis, we linked routinely collected data from the National Register of Medicinal Product Statistics (for redeemed prescriptions of all oral and non-oral forms of hormonal contraception since January 1995); Statistics Denmark (for educational attainment); the Danish Cancer Registry (for histologically verified cancers since 1943 and family history of premenopausal breast or ovarian cancer in mothers or sisters); the National Health Register (for hospital discharge diagnoses and surgeries since 1977) and the National Birth Register (includes all births since 1973 and for parous women: smoking status since 1991 and body mass index [BMI] since 2004). These national datasets could be linked accurately because since 1968 each resident in Denmark has a unique personal identification number in the Civil Registration System, and which is used by each Register.

The eligible study population (n = 1 904 094) consisted of all women aged 15 to 49 years living in Denmark from 1995 to 2014, except those entering Denmark after 1995. Exclusions were women with: treatment with ovarian stimulating drugs (Anatomical Therapeutic Chemical Classification code MG03G), venous thrombosis, hysterectomy or cancer (except non-melanoma skin cancer) before study entry. After exclusions, the study population (n = 1 853 542) was followed until the first diagnosis of cervical cancer (International Classification of Diseases [ICD] 10th revision[14] code C53); death; age 50 or 31 December 2014 (end of follow-up). Women were censored temporarily during pregnancy and for 6 months afterwards; and permanently at the date of venous thrombosis, ovarian stimulation drug treatment, hysterectomy or diagnosis of different cancer (except non-melanoma skin cancer).

2.1 | Statistical analysis

Analyses were conducted using SAS version 9.3 (SAS Institute, Inc, Cary, NC). During the study, women were categorised according to their use of hormonal contraception as current or recent (within 1 year of stopping); former (more than 1 year since stopping) or ever (any hormonal contraceptive use during the study period) users. Never users had no redeemed prescriptions for hormonal contraceptives recorded at study entry or during the study period. If a woman was a never user

on entry to the study and then subsequently redeemed a prescription for a hormonal contraceptive, her contraceptive status changed to current or recent use on the date the prescription was redeemed. Women could switch between current or recent and former user categories depending on prescriptions redeemed. Once a woman became a user of hormonal contraceptives, her contraceptive status could not return to never use. There were fewer periods of observation among never users because many of the women who were never users at study entry subsequently redeemed a prescription for a hormonal contraceptive, at which point their contraceptive status changed.

Age-specific incidence of cervical cancer per 100 000 person-years was calculated for the whole cohort. Using the age distribution of the entire cohort as the standard, age-standardised incidence rates of cervical cancer per 100 000 person-years were calculated for each of the user groups.

Poisson regression was used to calculate the cervical cancer risk among the different user groups, compared to never users. Adjusted rate ratios (hereafter described as relative risk [RR]) with corresponding 95% CIs allowed for time-varying covariates: hormonal contraceptive use, calendar year, age (15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49 years), education (elementary school only, high school only, further education excluding college/university, college/university, university education with research qualifications, unknown), tubal sterilisation (yes/no), endometriosis (yes/no), family history of premenopausal breast or ovarian cancer (yes/no) and parity (nulliparous, 1, 2, 3, 4, >4). Among parous women additional adjustments were made for BMI (<18.5, 18.5-25, >25-30, >30 kg/m^2) and smoking status (non-smoker, current, unknown) determined during pregnancy. We could not adjust for any aspects of sexual behaviour (such as age at first intercourse, number of partners or use of barrier contraceptives) since such information is not routinely collected by the national registers used.

Duration (for any hormonal contraception, and users of combined and progestin-only contraceptives separately) and time since last current use were examined, with tests for trend performed by the inclusion of the duration of time since last use variable as an ordinal variable and values set to the median in each category.[15] We examined tumour histology (coded using the International Classification of Diseases for Oncology, 3rd edition, ICD-O-3[16] all ending with behaviour invasive digit 3) as squamous (M8052, 8070, 8071, 8072, 8076, 8083); adenocarcinoma (M8140, 8144, 8262, 8310, 8380, 8441, 8480, 8490, 9110) and mixed/indeterminate/other (all other morphology codes provided with the C53 cancer registration).

We calculated risk estimates for different products in women followed in the study until their first switch in hormonal contraception, recognising that there might be lingering effects from previous use of hormonal contraceptives. Product-specific risk estimates were also calculated using 30 to 35 μg ethinylestradiol plus levonorgestrel preparations as the reference group. We performed exploratory analyses of risk estimates among the subset of women with complete contraceptive histories that is, those aged 15 on or after 1 January 1995. In this subset, we also examined the number, and effect of, receiving HPV vaccination (since these women were most likely to have been vaccinated).

It is possible that some women begin using, or restart, hormonal contraception because they experience symptoms such as heavy bleeding, which are subsequently attributed to cervical cancer. It is also possible that some women have a cervical smear around the time of beginning or restarting hormonal contraception, providing an opportunity for cervical cancer to be detected. In either situation, a short-term increase in events could be observed among current users of hormonal contraceptives, due to these factors rather than any biological effects of the contraceptives. To investigate whether such protopathic bias might have occurred, we undertook sensitivity analyses in which periods of observation were ignored for 1 year before the date of cervical cancer diagnosis. This resulted in the exclusion of 243 women with less than 1 year of observation before cancer diagnosis.

We did not adjust for multiple comparisons. For the full cohort, we calculated age-standardised absolute risks ($incidence_{exposed} - incidence_{unexposed}$) and the number needed to harm ($1/incidence_{exposed} - incidence_{unexposed}$).

3 | RESULTS

A total of 2339 incident cervical cancers occurred during 13 235 473 person-years among ever users of hormonal contraceptives and 1304 incident cervical cancers during 7 948 536 person-years among never users. Among ever users of hormonal contraceptives, the median duration of use was 5.02 years (interquartile range 2.03, 8.89 years); the mean duration was 5.87 years (SD = 4.51 years). Combined hormonal contraceptives accounted for 86% of all current or recent hormonal contraceptive use in the study (Table 1S). The relatively popular levonorgestrel-releasing intrauterine system (LNG-IUS) and desogestrel-containing progestin-only pills tended to be used by parous rather than nulliparous women, unlike other progestin-only products. Age-specific incidence of cervical cancer increased until age 40, whereupon it fell (Table 1). The age-adjusted incidence of cervical cancer in never users was 14.9 per 100 000 person-years and in ever users of any hormonal contraceptives 17.8 per 100 000 person-years (Table 2). Compared to never users, ever users of any hormonal contraceptives had an increased risk of cervical cancer: RR 1.19 (95% CI 1.10-1.29); driven by an increased risk among current or recent users: RR 1.30 (95% CI 1.20-1.42). Most of the risk associated with hormonal contraception arose from the use of combined contraceptives.

Examined separately, current or recent users of combined contraceptives had an increased risk of cervical cancer: RR 1.40 (95% CI 1.28-1.53), unlike current or recent users of progestin-only contraceptives: RR 0.91 (95% CI 0.78-1.07). Adjustment for BMI and smoking status among parous women did not materially change the risk estimates. For example, an increased cervical cancer risk was found among parous ever users of any hormonal contraceptives: RR 1.10 (95% CI 1.01-1.21) and current or recent users: RR 1.19 (95% CI

TABLE 1 Age-specific incidence per 100 000 of cervical cancer during the period 1995 to 2015

Age group (y)	Cervical cancer (n)	Person-years	Incidence per 100 000 person-years
15-19	<3[a]	3 155 580	n/a
20-24	136	2 878 558	4.7
25-29	455	2 784 600	16.3
30-34	744	2 987 372	24.9
35-39	878	3 213 356	27.3
40-44	825	3 265 173	25.3
45-50	603	2 901 373	20.8

[a]Data not available for presentation due to less than three events, incidence estimate therefore not available (n/a) and total person-years rounded to nearest five.

TABLE 2 Relative risk of cervical cancer in users of hormonal contraception (all women)

	Person-years	Cervical cancer (N)	Age-adjusted incidence/100000 person-years	Adjusted[a] relative risk (95% confidence interval)	Age-adjusted absolute risk (95% confidence interval)/100 000
Never use	7 948 536	1304	14.9	1.00	
Ever use (any hormonal)	13 235 473	2339	17.8	1.19 (1.10-1.29)	2.9 (1.8 to 4.1)
Former use (any hormonal)	4 412 259	872	16.0	1.02 (0.93-1.13)	1.1 (−0.4 to 2.5)
Current or recent use (any hormonal)	8 823 214	1467	19.8	1.30 (1.20-1.42)	4.9 (3.5 to 6.3)
Current or recent use (combined)	7 745 534	1269	21.7	1.40 (1.28-1.53)	6.8 (5.2 to 8.5)
Current or recent use (progestin-only)	1 077 679	198	14.5	0.91 (0.78-1.07)	−0.4 (−2.7 to 1.9)
Duration of current use (any hormonal contraception)					
≤1 y	1 262 551	173	23.9	1.37 (1.16-1.61)*	8.9 (5.1 to 12.8)
>1 to ≤5 y	4 055 910	462	17.2	1.14 (1.02-1.28)	2.3 (0.4 to 4.3)
>5 to ≤10 y	2 576 116	527	19.6	1.40 (1.24-1.57)	4.7 (2.6 to 6.8)
>10 y	928 636	305	23.0	1.55 (1.34-1.80)	8.1 (5.3 to 10.9)
Duration of current use (combined)					
≤1 y	1 183 528	150	22.8	1.34 (1.12-1.59)**	7.9 (3.8 to 12.0)
>1 to ≤5 y	3 641 233	410	19.9	1.25 (1.11-1.41)	5.0 (2.4 to 7.6)
>5 to ≤10 y	2 202 125	441	20.8	1.46 (1.28-1.65)	5.9 (3.3 to 8.5)
>10 y	718 648	268	26.2	1.76 (1.51-2.05)	11.3 (8.0 to 14.6)
Duration of current use (progestin-only)					
≤1 y	79 023	23	27.0	1.80 (1.19-2.71)***	12.1 (1.0 to 23.2)
>1 to ≤5 y	414 678	52	10.7	0.71 (0.53-0.94)	−4.2 (−7.4 to −1.0)
>5 to ≤10 y	373 991	86	22.0	1.16 (0.92-1.45)	7.1 (2.1 to 12.2)
>10 y	209 988	37	10.6	0.75 (0.54-1.06)	−4.3 (−7.9 to −0.8)
Time since last current use of any hormonal contraception					
>1 to ≤5 y	2 412 582	465	16.4	1.09 (0.97-1.22)¶	1.5 (−0.3 to 3.3)
>5 to ≤10 y	1 360 077	292	16.0	1.03 (0.90-1.18)	1.1 (−1.4 to 3.5)
>10 y	637 600	115	11.5	0.79 (0.65-0.97)	−3.4 (−6.9 to 0.0)

*p-Trend <.001, **p-Trend <.001, ***p-Trend = .303,
¶p-Trend <.001.
[a]Adjusted for: calendar year, education, age, parity, family history of breast or ovarian cancer, tubal sterilisation and endometriosis.

1.08-1.31), but not among former users: RR 0.98 (95% CI 0.88-1.09) (data not shown).

In analyses of both any hormonal and combined contraceptives, there was a trend of increasing cervical cancer risk with duration of current use. This relationship was not seen among users of progestin-only products. When the entire dataset was examined, there was no increased risk of cervical cancer among women who were more than 1 year since last current use (Table 2). However, when the data were

TABLE 3 Relative risk of cervical cancer in hormonal contraceptive users by time since last use and duration of use (all women)

	Time since last current use								
	>1 to ≤5 y			>5 to ≤10 y			>10 y		
Duration of use	Person-years	Events	RR (95% CI)[a]	Person-years	Events	RR (95% CI)*	Person-years	Events	RR (95% CI)[a]
≤1 y	659 103	104	1.07 (0.87-1.31)	456 734	84	1.01 (0.81-1.28)	303 177	64	1.06 (0.81, 1.40)
>1 to ≤5 y	1 028 947	184	1.20 (1.01-1.42)	620 549	141	1.25 (1.03-1.52)	296 198	42	0.70 (0.50, 0.97)
>5 y	726 532	177	1.55 (1.27-1.89)	282 794	67	1.37 (1.03-1.83)	38 225	9	1.29 (0.65, 2.56)
Total	2 414 582	465		1 360 077	292		637 600	115	

[a]Adjusted for: calendar year, education, age, parity, family history of breast or ovarian cancer, tubal sterilisation and endometriosis.

stratified by duration of use and time since last use, there was evidence that the risk among women with prolonged use may take longer to disappear (up to 10 years) than the risk among women with shorter-term use (Table 3).

The overall risk estimates in the subset of women followed until their first switch in hormonal contraceptive were of similar magnitude to those seen in the full cohort (Table 4). We had insufficient data to calculate risk estimates for some of the products used including vaginal rings and contraceptive patches. Overall, there was little evidence of major differences in risk between combined products containing different progestins. Analyses where 30 to 35 μg ethinylestradiol plus levonorgestrel products formed the referent group (Table 2S), and when product-specific estimates were calculated among the full cohort (Table 3S), also found few differences between products. In both analyses, current or recent users of the LNG-IUS had a reduced cervical cancer risk when compared to current or recent users of 30 to 35 μg ethinylestradiol plus levonorgestrel products.

Larger, but very imprecise, point estimates were observed in the exploratory analysis among women with full contraceptive history (-Table 4S). Former users of any hormonal contraception had an increased risk of cervical cancer in this subset analysis: RR 4.35 (95% CI 1.57-12.00). More than three-quarters of former users had stopped within the previous 5 years (data not shown). In this subset, current or recent use of progestin-only products was associated with increased cervical cancer risk: RR 3.38 (95% CI 1.13-10.10). There was little evidence of differences in the risk estimates of combined products containing different progestins when compared against 30 to 35 μg ethinylestradiol plus levonorgestrel products (Table 4S). More never users in the full contraceptive history subset had received an HPV vaccination than ever users (24.0% vs 9.7% periods of observation, respectively) (Table 5S). The risk estimates in Table 4S changed very little after also adjusting for HPV vaccination (data not shown).

Approximately three-quarters of the cervical cancers were squamous (Table 5). Current or recent users of any hormonal contraception had an increased risk of both adenocarcinoma and squamous tumour types.

Sensitivity analysis which excluded periods of observation 1 year before diagnosis in the full cohort found that short duration (<1 year) current use of combined or progestin-only hormonal contraceptives was no longer positively associated with cervical cancer (Table 6S). A similar sensitivity analysis of women followed up until their first switch in hormonal contraception also found short-term current use of any hormonal and combined contraceptives did not increase the risk of cervical cancer (Table 7S).

Age-adjusted absolute risks were calculated for the main patterns of contraceptive use in the entire cohort (Table 2). The age-adjusted absolute risk of cervical cancer among current or recent use of combined contraceptives was 6.8 per 100 000 (95% CI 5.2-8.5) person-years; approximately one extra case of cervical cancer for every 14 706 women using combined contraceptives for 1 year.

4 | DISCUSSION

In this cohort study of mostly women unvaccinated for HPV, current or recent use of any hormonal contraception and combined contraception, but not progestin-only contraception, was associated with an increased risk of cervical cancer; an effect which strengthened with increasing duration of use. The increased risk of cervical cancer among women with prolonged use appeared to take up to 10 years to disappear after stopping. Where there was sufficient use of products to permit analysis, there was little evidence of material differences in risk between different combined preparations. Current or recent use of any hormonal contraception was positively associated with both squamous and adenocarcinoma types of cervical cancer.

Our results indicate that currently used combined oral contraceptives are associated with a similar pattern of cervical cancer risk as that of older preparations,[8] at least among women not vaccinated against HPV. We had insufficient data to assess robustly the risk associated with combined contraceptive patches or vaginal rings. Most studies published since the International Collaboration's publication have investigated ever use of combined oral contraception.[10,11,17-24] Several reported an increased risk of cervical cancer with prolonged use[10,11,17,18] and a waning risk with increasing time since last use.[11,17,21,24,25] None of the other studies provided product-specific estimates. We found little evidence of major differences in risk between combined products containing different progestins.

Based on 10 studies (out of 24 overall), the International Collaboration found an increased risk of cervical cancer in women with 5 or

TABLE 4 Relative risk of cervical cancer among users of different hormonal contraceptives in women followed up until first switch in hormonal contraceptive

	Person-years	Cervical cancer (N)	Adjusted[a] relative risk (95% confidence interval)
Never use	7 948 536	1304	1.00
Ever use (any hormonal)	7 127 336	1135	1.18 (1.08-1.28)
Former use (any hormonal)	2 540 968	491	1.04 (0.93-1.17)
Current or recent use (any hormonal)	4 586 368	644	1.29 (1.16-1.42)
Current or recent use (combined)	4 313 847	603	1.36 (1.22-1.51)
Current or recent use (progestin-only)	272 521	41	0.77 (0.57-1.06)
Current or recent use of combined hormonal contraception			
Oral			
Norethisterone 50 μg EE	36 407	18	2.69 (1.68-4.28)
Levonorgestrel 50 μg EE	47 171	15	1.59 (0.95-2.64)
Norethisterone 30-35 μg EE	115 988	23	1.73 (1.14-2.63)
Levonorgestrel 30-35 μg EE	518 647	123	1.48 (1.23-1.79)
Desogestrel 20-30 μg EE	988 333	112	1.21 (0.99-1.48)
Gestodene 20-35 μg EE	1 885 998	240	1.31 (1.13-1.52)
Drospirenone 20-35 μg EE	188 850	9	1.13 (0.58-2.19)
Norgestimate 35 μg EE	375 464	48	1.35 (1.01-1.80)
Cyproterone 30 μg EE	142 001	14	1.01 (0.59-1.71)
Estradiol valerate, dienogest	1010	<3	n/a
Non-oral			
Patch	2250	<3	n/a
Vaginal ring	11 730	<3	n/a
Current or recent use of progestin-only contraception			
Oral			
Norethisterone	66 790	10	0.75 (0.40-1.40)
Levonorgestrel	6955	<3	n/a
Desogestrel	12 110	<3	n/a
Non-oral			
MPA depot	7315	<3	n/a
Implant	10 555	<3	n/a
LNG-IUS	168 801	27	0.76 (0.52-1.11)
Duration of current use (any hormonal contraception)			
≤1 y	1 059 532	135	1.30 (1.08-1.56)
>1 to ≤ 5 y	2 309 695	241	1.12 (0.97-1.29)
>5 to ≤10 y	960 337	185	1.43 (1.21-1.70)
>10 y	256 804	83	1.66 (1.31-2.11)
Duration of current use (combined)			
≤1 y	1 000 606	120	1.29 (1.07-1.57)
>1 to ≤5 y	2 144 034	223	1.24 (1.06-1.44)
>5 to ≤10 y	919 330	177	1.48 (1.24-1.75)
>10 y	249 877	83	1.69 (1.33-2.15)
Duration of current use (progestin-only)			
≤1 y	58 926	15	1.46 (0.87, 2.42)
>1 to ≤5 y	165 660	18	0.56 (0.35, 0.89)
>5 to ≤10 y	41 007	8	0.96 (0.48, 1.93)
>10 y	6930	<3	n/a

TABLE 4 (Continued)

	Person-years	Cervical cancer (N)	Adjusted[a] relative risk (95% confidence interval)
Time since last current use of any hormonal contraception			
>1 to ≤5 y	1 267 925	225	1.08 (0.93-1.25)
>5 to ≤10 y	808 397	180	1.10 (0.93-1.30)
>10 y	464 646	86	0.85 (0.67-1.08)

Note: <3: data not available for presentation due to less than three events, estimate therefore not available (n/a) and total person-years rounded to nearest five.

Abbreviations: EE, ethinylestradiol; LNG-IUS, levonorgestrel-releasing intrauterine system.

[a]Adjusted for: calendar year, age, education, parity, family history of breast or ovarian cancer, tubal sterilisation and endometriosis.

TABLE 5 Relative risk of different histological types of cervical cancer associated with hormonal contraception (all women)

Histology	Person-years	Cervical cancer (N)	Adjusted[a] relative risk (95% confidence interval)
Squamous		2720	
Never use	7 948 536	991	1.00
Current or recent use	8 823 214	1090	1.31 (1.19-1.44)
Former use	4 412 259	639	1.03 (0.92-1.15)
Adenocarcinoma		626	
Never use	7 948 536	209	1.00
Current or recent use	8 823 214	257	1.29 (1.05-1.60)
Former use	4 412 259	160	0.98 (0.77-1.24)
Mixed/indeterminate/others		297	
Never use	7 948 536	104	1.00
Current or recent use	8 823 214	120	1.29 (0.95-1.74)
Former use	4 412 259	73	1.08 (0.76-1.52)

[a]Adjusted for: calendar year, age, education, parity, family history of breast or ovarian cancer, tubal sterilisation and endometriosis.

more years of progestin-only injectable contraceptive use: RR 1.22 (95% CI 1.01-1.46).[8] Risk estimates for progestin-only oral contraceptives could not be calculated. The Johannesburg Cancer Case Control Study examined progestin-only injectable use and cervical cancer and found that exclusive users of progestin-only injectables less than 10 years previously were more likely to be diagnosed with cervical cancer than never users of hormonal contraceptives: OR 1.58 (95% CI 1.16-2.15).[21] When time since last use and duration of use were examined simultaneously, cervical cancer risk diminished with increasing time since last use, without a relationship to duration of use.[21] The results from both of these studies[8,21] suggest an increased risk of cervical cancer among progestin-only injectable users. The use of MPA depot was rare in our cohort. Our main analyses did not reveal an increased risk with current or recent use of any progestin-only contraceptives regardless of route of administration. Neither was there a relationship with duration of current use. The exploratory subgroup analysis of women with a complete contraceptive history did observe increased (but very imprecise) risk estimates for progestin-only contraceptives, including for current or recent use of progestin-only products. This estimate may have been affected by a lingering effect of previous use of combined contraceptives. Very few women in our study used progestin-only products only and so we had limited statistical power to detect effects for some of the progestin-only products. The absence of cervical cancer risk among LNG-IUS users supports findings from a nationwide cohort study of Finnish women aged 30-49 years using the LNG-IUS for menorrhagia, which found a standardised incidence ratio (SIR) of 0.90 (95% CI 0.69-1.15) for all cervical cancer and SIR 1.18 (95% CI 0.74-1.79) for cervical adenocarcinoma.[26]

Strengths of our study include the ability to examine all types of hormonal contraceptives used between 1995 and 2014 among a nearly whole nation cohort of more than 1.8 million women of reproductive age, observed for over 21 million person-years. Information about both redeemed prescriptions for hormonal contraceptives and incident cervical cancers are routinely collected prospectively by the National Registers, thus avoiding information bias. When considering specific products, our main risk estimates were calculated among women followed until their first switch in hormonal contraceptive in the study, to reduce the possibility that a risk estimate for a particular product might reflect lingering effects from another previously used hormonal contraceptive(s). There was little evidence of important differences in risk estimates for combined contraceptives containing different progestins. Compatible results were found in the exploratory analyses of women with a full contraceptive history, although the risk estimates were much less precise because they were based on fewer cervical cancers (n = 285) and less periods of observation (25%) than

in the main analysis. Although we could adjust for several possible confounders, we lacked information about cervical screening, age at first intercourse or number of sexual partners so residual confounding could have occurred. That said, the International Collaboration found similar patterns of risk among women likely to have been screened as among those not screened, and in the subgroup of women who tested positive for high-risk HPV compared to all women studied.[8] Information about lifetime number of sexual partners was available in all of the case-control but none of the cohort studies included in the pooled analysis. However, there was little difference in results using all studies, compared to the findings of only case-control studies that is, the patterns of increased cervical cancer risk associated with oral contraceptive use persisted after adjustment for sexual behaviour. Adjustment for HPV serology did not materially change the cervical cancer and oral contraceptive use findings from the European Prospective Investigation into Cancer and Nutrition.[23] We could adjust for BMI and smoking status only among parous women, and then for only part of the follow-up period. Although these adjustments did not substantially alter the risks estimates, again it is possible that our results are subject to residual confounding. Previous studies have suggested that users of combined oral contraceptives are more likely to smoke than non-users of these contraceptives.[10,24] If this remains the case, incomplete adjustment for smoking may have overestimated the risk of cervical cancer among combined contraceptive users.

Hormonal contraceptives may exert molecular effects through which persistent HPV infection leads to cervical cancer. For example, oestrogen and progestin might promote HPV 16 E6 and E7 oncogene expression, stimulating p53 tumour suppressor gene degradation and viral DNA integration and transformation of cells to induce cancer development.[8,23,27] Other postulated mechanisms include, changed cervical susceptibility to HPV infection, or altered HPV infection natural history leading to reduced clearance.[8,23,27] It is not clear whether and how these mechanisms might be different for progestin-only contraceptives.

The Danish childhood immunisation programme for 12-year-old girls has included HPV vaccination since 2009.[28] Thus, our findings reflect the risks associated with hormonal contraception in a predominantly unvaccinated cohort. The absence of material change after adjusting for HPV vaccination in the full contraceptive subset was likely due to the small proportion of person-time attributable to HPV vaccinated women. Given recent evidence from Sweden that girls and women aged 10 to 30 who received the quadrivalent HPV vaccination had a substantially reduced risk of invasive cervical cancer,[29] we await the opportunity to determine whether HPV vaccination within our cohort reduces cervical cancer incidence. Such an effect would increase the number needed to harm from combined oral contraceptive use.

In our cohort of women mostly unvaccinated for HPV, we estimate that one extra case of cervical cancer occurred in our cohort for every 14 706 women who used contemporary combined contraception for 1 year. The absolute risk will be higher in countries where cervical cancer is more common than in Denmark; countries where comprehensive screening and HPV vaccination programmes are often absent and where perhaps two-thirds of all hormonal contraceptive users live. Women should be informed of the association between contemporary combined contraception and cervical cancer, an effect which is enhanced by prolonged use but which disappears some years after stopping. Such information should be balanced against high levels of protection against pregnancy and its associated mortality and morbidity, and other important non-contraceptive benefits including large sustained protection against ovarian[30] and endometrial[31] cancer.

Our results indicate that currently available combined contraceptives continue to be positively associated with the risk of cervical cancer, at least among women not vaccinated against HPV. Women wishing to use this method of contraception need to be informed of this risk and encouraged to participate in a cervical screening programme, if available. They should also be alert to any symptoms indicative of cervical cancer, and report these promptly to their health care provider. Our findings also reinforce the urgent public health need for global interventions to prevent cervical cancer.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The study data are held with the secure data depository at Statistics Denmark, permissions to access can only be granted by Statistics Denmark (https://www.dst.dk/en/TilSalg/Forskningsservice). Further details that support the findings of this study are available from the corresponding author upon request.

ETHICS STATEMENT

Ethical approval is not required for register-based studies in Denmark. Approval was obtained from the Health Data Board and Danish Data Protection Agency. The data were analysed (by SF) and held within the secure data repository at Statistics Denmark, with personal identification numbers encrypted.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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